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# Veno-venous extracorporeal CO<sub>2</sub> removal for the treatment of severe respiratory acidosis: pathophysiological and technical considerations

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## Abstract

**Introduction:** While non-invasive ventilation aimed at avoiding intubation has become the modality of choice to treat mild to moderate acute respiratory acidosis, many severely acidotic patients (pH <7.20) still need intubation. Extracorporeal veno-venous CO<sub>2</sub> removal (ECCO<sub>2</sub>R) could prove to be an alternative. The present animal study tested in a systematic fashion technical requirements for successful ECCO<sub>2</sub>R in terms of cannula size, blood and sweep gas flow.

**Methods:** ECCO<sub>2</sub>R with a 0.98 m<sup>2</sup> surface oxygenator was performed in six acidotic (pH <7.20) pigs using either a 14.5 French (Fr) or a 19Fr catheter, with sweep gas flow rates of 8 and 16 L/minute, respectively. During each experiment the blood flow was incrementally increased to a maximum of 400 mL/minute (14.5Fr catheter) and 1000 mL/minute (19Fr catheter).

**Results:** Amelioration of severe respiratory acidosis was only feasible when blood flow rates of 750 to 1000 mL/minute (19Fr catheter) were used. Maximal CO<sub>2</sub>-elimination was 146.1 ± 22.6 mL/minute, while pH increased from 7.13 ± 0.08 to 7.41 ± 0.07 (blood flow of 1000 mL/minute; sweep gas flow 16 L/minute). Accordingly, a sweep gas flow of 8 L/minute resulted in a maximal CO<sub>2</sub>-elimination rate of 138.0 ± 16.9 mL/minute. The 14.5Fr catheter allowed a maximum CO<sub>2</sub> elimination rate of 77.9 mL/minute, which did not result in the normalization of pH.

**Conclusions:** Veno-venous ECCO<sub>2</sub>R may serve as a treatment option for severe respiratory acidosis. In this porcine model, ECCO<sub>2</sub>R was most effective when using blood flow rates ranging between 750 and 1000 mL/minute, while an increase in sweep gas flow from 8 to 16 L/minute had less impact on ECCO<sub>2</sub>R in this setting.

## Introduction

Non-invasive ventilation (NIV) has become the modality of choice to treat mild to moderate respiratory acidosis (pH ≥7.20) due to chronic obstructive pulmonary disease (COPD) exacerbation, since it has been shown to avoid intubation and intubation-related complications, resulting in reduced ICU-mortality [1]. However, real-life observations have revealed high rates of both intubation and mortality in patients with COPD exacerbation and severe acute hypercapnic respiratory failure [2-4]. This is related to severe

respiratory acidosis, well-established contraindications of NIV, lack of staff training and the presence of co-morbidities hindering the successful application of NIV [5,6].

This has led to the attempt of extracorporeal carbon dioxide (CO<sub>2</sub>) removal (ECCO<sub>2</sub>R) in patients presenting with acute hypercapnic respiratory failure. ECCO<sub>2</sub>R systems have been successfully used to reduce invasiveness of mechanical ventilation and, therefore, ventilator-induced lung injury in acute respiratory distress syndrome (ARDS) patients [7-12]. Recently, ECCO<sub>2</sub>R by means of a pumpless, arterio-venous extracorporeal lung-assist has been shown to preclude the need for intubation and invasive mechanical ventilation in a case-control study in COPD patients with acute-on-chronic respiratory failure [13]. In addition, previous research has demonstrated that this technique is capable of eliminating approximately 50% of the calculated CO<sub>2</sub> production, with rapid normalization

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of respiratory acidosis [14]. Importantly, these systems are driven by the arterio-venous pressure gradient; thus, cannulation of arterial vessels (most commonly the femoral artery), coupled with cannulation of the corresponding vein on the contralateral limb, is necessary for driving the system [13-15]. Based on these preconditions, there are clearly defined contraindications and several complications directly related to arterial cannulation, such as bleeding, hematoma or aneurysm at the insertion site, and ischemia and/or compartment syndrome of the lower limb [15,16].

Interestingly, a recent study reported the successful application of a pump-driven veno-venous system using a 15.5 French (Fr) dual-lumen catheter with a mean blood flow of 431 ml/minute [17]. Even though this was a pilot study testing the feasibility of this new approach, the study showed the potential of these veno-venous systems to improve respiratory acidosis without requiring arterial cannulation. However, patients only had moderate respiratory acidosis, and it remains unclear how these results translate to more severe respiratory acidosis. Accordingly, clinical experience suggests that substantially higher flow rates are needed to correct severe respiratory acidosis (pH <7.2) [18]. In this regard, the physiological relationships between cannula size, blood flow, sweep gas flow and gas transfer capacity, respectively, are still largely unknown. For this reason, more physiological data on these issues are needed before the promising technique of miniaturized veno-venous ECCO<sub>2</sub>R can be tested in a broader clinical setting. Therefore, we set up an animal study that aimed to elucidate the relationships between cannula size, blood flow and sweep gas flow, respectively, in pigs with experimentally-induced severe respiratory acidosis that mimicked severe acute hypercapnic respiratory failure with pH values between 7.0 and 7.2.

## Material and methods

### Extracorporeal CO<sub>2</sub> removal techniques

For ECCO<sub>2</sub>R a pump assisted lung protection (PALP) System® (Maquet Cardiopulmonary Care, Rastatt, Germany) based on the Cardiohelp® platform was used. The oxygenator has an area of 0.98 m<sup>2</sup> with a poly methylpentene membrane lacking heat exchange fibers. The priming volume of the whole system is 247 ml. The PALP system® was primed with normal saline solution. Heparin (1,000 IE) was added to the running system.

For venous access, a 14.5Fr hemodialysis catheter (Fresenius Medical Care, Bad Homburg Germany) was used during Experiments 1 and 2, while a 19Fr Bicaval Avalon ELITE Dual Lumen Cannula® (Maquet Cardiopulmonary Care, Rastatt, Germany) was implanted for Experiments 3, 4 and 5. Pigs were anticoagulated with heparin during extracorporeal treatment. For all experiments, the sweep gas flow was applied with 100% oxygen by a Flow-i Anesthesia Delivery System (Maquet Critical Care, Solna,

Sweden); in a subset of animals the sweep gas flow was provided with room air.

### Animal model

The study was approved by the Animal Research Committee of Uppsala University in Sweden (ethical approval number: C265/12). Pigs (body weight = 39.8 ± 2.9 kg) were anesthetized with IV ketamine 25 to 50 mg/kg/hour, midazolam 90 to 180 µg/kg/hour, fentanyl 3 to 6 µg/kg/hour and rocuronium 2.5 to 5.0 mg/kg/hour. The trachea was intubated with a cuffed endotracheal tube (inner diameter, 7 mm). The pigs were ventilated with a Servo-i ventilator (Maquet Critical Care, Solna, Sweden). Body temperature was kept at 37°C throughout the whole study period by the use of a warm blanket. Arterial blood was taken from the left carotid artery. The estimated CO<sub>2</sub> production is about 7 ml/kg/minute in pigs [19], that is, a CO<sub>2</sub> production of approximately 280 ml/minute, which is comparable to an adult human.

### Study design

ECCO<sub>2</sub>R was performed in six pigs following intubation, mechanical ventilation and induction of respiratory acidosis by increased dead space ventilation. In detail, anatomical dead space was increased by adding a further tube between the endotracheal tube and the 'Y' piece of the ventilator circuit. The length of the additional tube was titrated until respiratory acidosis was induced with a pH value of 7.0 to 7.1. Pigs were ventilated in a volume controlled mode with a tidal volume of 360 ml, a positive end expiratory pressure (PEEP) of 6 cm H<sub>2</sub>O and a breathing frequency of 15/minute. Dead space fractions and CO<sub>2</sub> elimination were measured with a NICO monitor (Philips, Wallingford, CT, USA), where airway flow and CO<sub>2</sub> signals were monitored by mainstream sensors placed between the endotracheal tube and the 'Y' piece of the ventilator circuit. Dead space was computed as PCO<sub>2</sub>et-PeCO<sub>2</sub>/PCO<sub>2</sub>et, where PCO<sub>2</sub>et represents the end-tidal partial pressure of CO<sub>2</sub> and PeCO<sub>2</sub> the mixed expired CO<sub>2</sub>. Dead space fraction was measured in the first pig by the Bohr equation, with a resulting fraction of 0.85. This dead space fraction was subsequently maintained for the entire duration of the experimental period.

Five experiments were performed in each pig in a standardized fashion. First, ECCO<sub>2</sub>R was performed via a 14.5Fr hemodialysis catheter inserted into the right jugular vein (experiments 1 and 2). Subsequently, ECCO<sub>2</sub>R was performed via the 19Fr catheter following re-catheterization of the same right jugular vein (experiments 3, 4, and 5). Correct placement of the 19Fr cannula was confirmed by echocardiography. Equal conditions were used across all experiments (lasting at least 60 minutes), with each experiment starting at the pre-determined acidotic conditions.

During experiments 1 to 4, blood flow rates were increased in a stepwise fashion, while sweep gas flow was maintained (Table 1). Each step lasted 15 minutes in order to achieve equilibrium conditions, with all measurements taken at the end of this 15-minute period.

During experiment 5, sweep gas flow was changed by increasing flow in a stepwise approach (Table 1), while blood flow was maintained at a rate of 1,000 ml/min. Each step lasted 15 minutes in order to achieve equilibrium conditions.

### CO<sub>2</sub> and blood gas measurement

CO<sub>2</sub> was measured in the mainstream of the exhaust/sweep-gas outlet of the oxygenator by the Vaisala Carbo-cap GM 70 (Vaisala, Bonn, Germany). A water trap was integrated into the circuit before CO<sub>2</sub> measurement. CO<sub>2</sub> removal was calculated by multiplying the sweep gas flow with CO<sub>2</sub> in Vol% in the exhaust/sweep-gas outlet. CO<sub>2</sub> was measured with 0.04 Vol% in fresh air. Blood gas analysis was performed with an ABL 800, Radiometer, (Copenhagen, Denmark).

### Statistics

For statistical analysis, GraphPad Prism 5 for Macintosh computer (La Jolla, CA USA) was used. Data were tested for normality using the Kolmogorov-Smirnov test with a cut-off *P* value of <0.05. Normally-distributed data are expressed as mean and standard deviation.

### Results

ECCO<sub>2</sub>R was most effective with the 19Fr catheter at higher blood flow levels (experiments 3 and 4; Figure 1), with no clear difference between different sweep gas flow (8 versus 16 L/minute) conditions. In contrast, ECCO<sub>2</sub>R was less efficient with the 14.5Fr catheter (experiments 1 and 2; Figure 1). As a consequence, partial pressure of CO<sub>2</sub> in arterial blood (PaCO<sub>2</sub>) progressively decreased with increasing blood flow when the 19Fr catheter, but not the 14.5Fr catheter, was used (Figure 2). Similarly, pH values progressively increased in proportion with blood

flow with the 19Fr catheter, but not the 14.5Fr catheter (Figure 3). Of note, non-acidotic blood gas values were only achieved with 19Fr catheters at blood flow rates ranging from 750 to 1,000 ml/minute. Detailed data on CO<sub>2</sub> elimination and related blood gas values relative to different blood flow levels at a sweep gas flow of 16 L/minute are provided in Tables 2 and 3 and Additional file 1, respectively. The absolute values of CO<sub>2</sub> elimination were normalized to the partial pressure of CO<sub>2</sub> in venous blood (PvCO<sub>2</sub>) and a partial pressure of CO<sub>2</sub> (PCO<sub>2</sub>) value of 45 mmHg according to Wearden *et al.* [20] and are provided in Figure 4.

Corresponding data for different sweep gas flows were comparable, where a higher sweep gas flow of 16 L/minute resulted in only a slightly more effective ECCO<sub>2</sub>R compared to a lower sweep gas flow of 8 L/minute (Tables 2 and 3 and Additional file 1). However, a sweep gas flow below 6 L/minute resulted in less effective ECCO<sub>2</sub>R when large (19Fr) catheters were used at high blood flow levels (1,000 ml/minute) (Figure 5). The extracorporeal system was more effective with higher PvCO<sub>2</sub> and lower blood flow levels and a longer oxygenator contact time, as demonstrated by a lower PCO<sub>2</sub> post-oxygenator (Figure 6).

In three pigs, the sweep gas flow was switched from 100% oxygen to room air at the end of experiment 5, with blood flow rates of 1,000 ml/minute. This resulted in a further increase in CO<sub>2</sub> removal (150 ± 26.6 versus 159.8 ± 22.6 ml/minute).

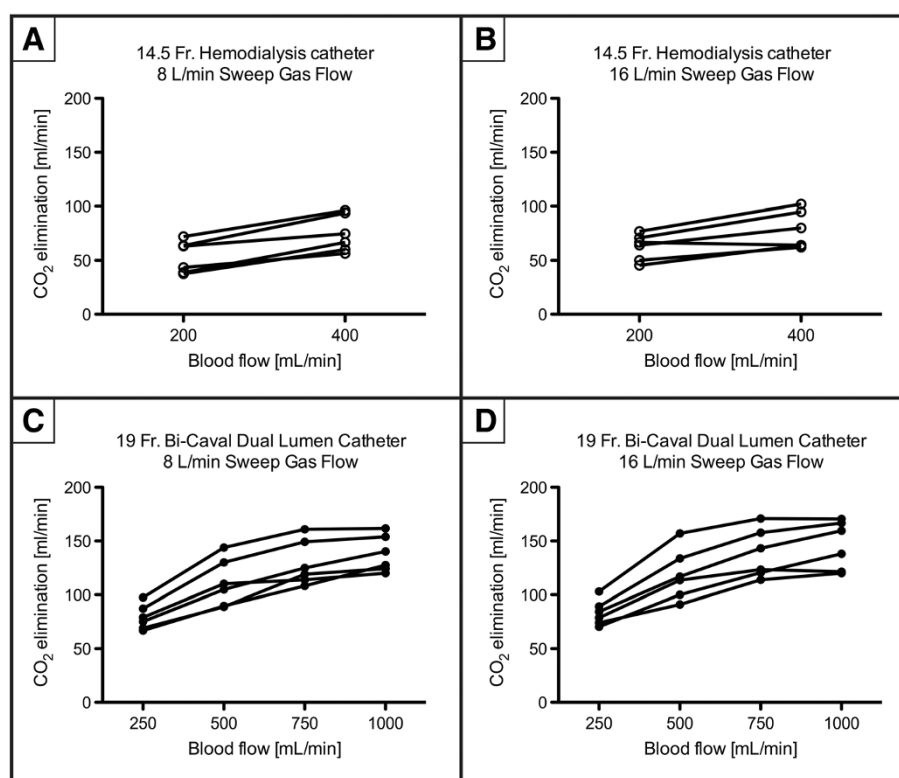
### Discussion

The present porcine study indicates that pump-driven veno-venous ECCO<sub>2</sub>R can normalize pH values and reduce PaCO<sub>2</sub> in severe, life-threatening respiratory acidosis under constant ventilatory support. In addition, the present study suggests that a blood flow of 750 to 1,000 ml/minute is needed to achieve these results, since pH values remained acidotic at lower blood flow rates.

In particular, the severe respiratory acidosis in the model used in this study could not be sufficiently corrected either by ECCO<sub>2</sub>R at a blood flow of 200 to

**Table 1 Experimental set-up (experiments 1 to 5)**

Parameter	Experiment 1	Experiment 2	Experiment 3	Experiment 4	Experiment 5
Catheter size (French)	14.5	14.5	19	19	19
Sweep gas flow (L/min)	8	16	8	16	2 to 10
Blood flow (ml/min)	0	0	0	0	1,000
	200	200	250	250	
	400	400	500	500	
			750	750	
			1,000	1,000	



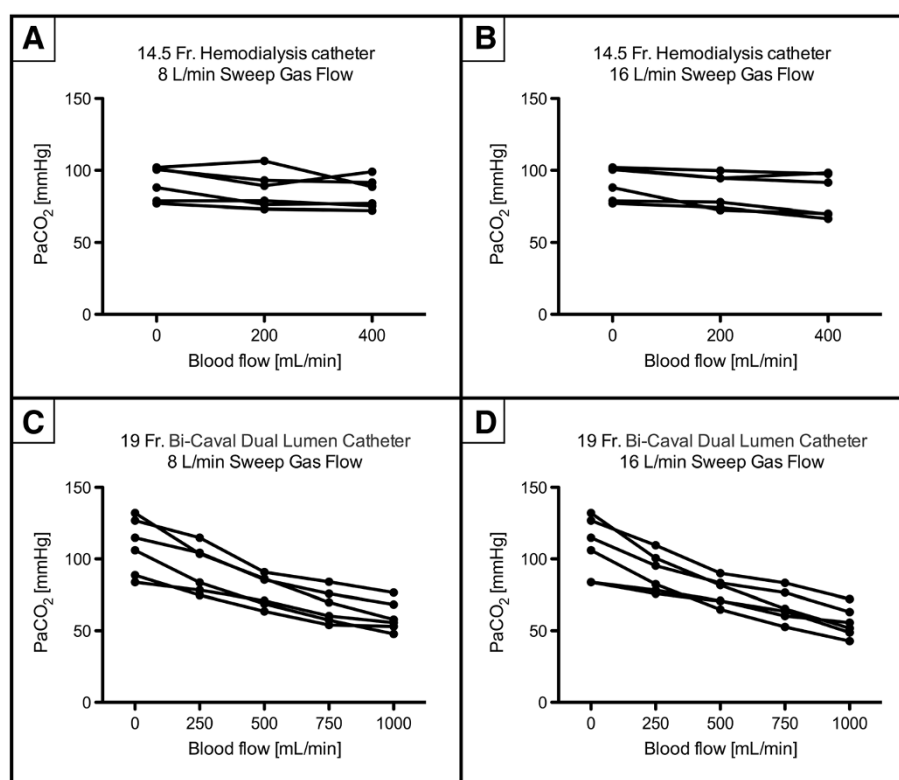
**Figure 1 Elimination of carbon dioxide (CO<sub>2</sub>) depending on blood flow.** **A)** 14.5Fr catheter; 8 L/minute sweep gas flow. **B)** 14.5Fr catheter; 16 L/minute sweep gas flow. **C)** 19Fr catheter; 8 L/minute sweep gas flow. **D)** 19Fr catheter; 16 L/minute sweep gas flow. Fr, French.

400 ml/minute using the 14.5Fr catheter, or with blood flow rates of 500 ml/minute using the 19Fr cannula. In contrast, severe respiratory acidosis was normalized by veno-venous ECCO<sub>2</sub>R using the 19Fr catheter and a blood flow rate of 1,000 ml/minute, even though a blood flow of 750 ml/minute was sufficient in 50% of the animals. This finding contrasts with a recent study in human patients, where the application of a pump-driven veno-venous system using a 15.5Fr dual-lumen catheter was successful with a mean blood flow of 431 ml/minute [17]. Importantly, however, the mean pH in that study was around 7.25, thus considerably higher compared to the pH in the present study. Thus, based on the current findings, it remains questionable whether more acidotic pH values could also be successfully corrected by lower blood flow rates, although the 15.5Fr catheter has a more favorable design compared to the 14.5Fr Shaldon catheter. Therefore, using low-diameter catheters and low blood flow rates, pump-driven veno-venous ECCO<sub>2</sub>R may be primarily feasible in patients with mild to moderate respiratory acidosis. This may be aimed at reducing aggressiveness of invasive ventilation as originally, and also recently, described in patients with ARDS [7,9,12,21,22].

Interestingly, the ECCO<sub>2</sub>R capacity of the system used in the present study was in line with previous findings

that were also derived from an animal study, where a removal-capacity up to 150 ml CO<sub>2</sub>/minute could be achieved with a blood flow of 1,000 ml/minute and an 18Fr catheter [23]. In accordance with the present trial, lower blood flow rates resulted in less efficient ECCO<sub>2</sub>R. In clear contrast, however, the mentioned trial provided evidence that ventilation parameters could be reduced following ECCO<sub>2</sub>R, but again, animals were not as severely acidotic as those in the present study. Therefore, the current study provides the first evidence that even severe acidosis can be successfully managed by ECCO<sub>2</sub>R and, in agreement with our clinical experience, this was only feasible with catheters that allowed blood flow rates of 750 to 1,000 ml/minute.

Since intensive care specialists are familiar with 14.5Fr hemodialysis catheters, it would be reasonable to test whether these catheters also qualify for ECCO<sub>2</sub>R. However, the maximal blood flow through these catheters is physiologically restricted to approximately 400 ml/minute. Furthermore, catheters specifically designed for ECCO<sub>2</sub>R aim to avoid recirculation [24,25]; this is particularly evident if the PCO<sub>2</sub> of the venous blood, which is directed towards the oxygenator, is lower than arterial PCO<sub>2</sub>. Of note, recirculation was obvious when hemodialysis catheters were used, even with the lowest blood flow



**Figure 2** Partial pressure of arterial carbon dioxide (PaCO<sub>2</sub>) depending on blood flow. **A)** 14.5Fr catheter; 8 L/minute sweep gas flow. **B)** 14.5Fr catheter; 16 L/minute sweep gas flow. **C)** 19Fr catheter; 8 L/minute sweep gas flow. **D)** 19Fr catheter; 16 L/minute sweep gas flow. Fr, French.

rates, demonstrated by a much lower CO<sub>2</sub> before oxygenator than in the arterial blood (Figure 6A and B). In contrast, the specifically designed 19Fr catheter produced no significant recirculation, represented by higher CO<sub>2</sub> before oxygenator than in arterial blood (Figure 6C and D). Therefore, (1) blood flow rates and (2) the specific technical design of the catheter that prevents recirculation are the main determinants of successful ECCO<sub>2</sub>R. Furthermore, CO<sub>2</sub> elimination of the oxygenator depends closely on the diffusion gradient of CO<sub>2</sub> between venous blood and the sweep gas. Therefore, with a higher CO<sub>2</sub> content in venous blood, more CO<sub>2</sub> will be eliminated, which has to be taken into consideration at the beginning of the experiments, when PvCO<sub>2</sub> is highest. Furthermore, PaCO<sub>2</sub> and PvCO<sub>2</sub> were slightly higher in the low-flow group with the 19Fr than with the 14.5Fr catheter.

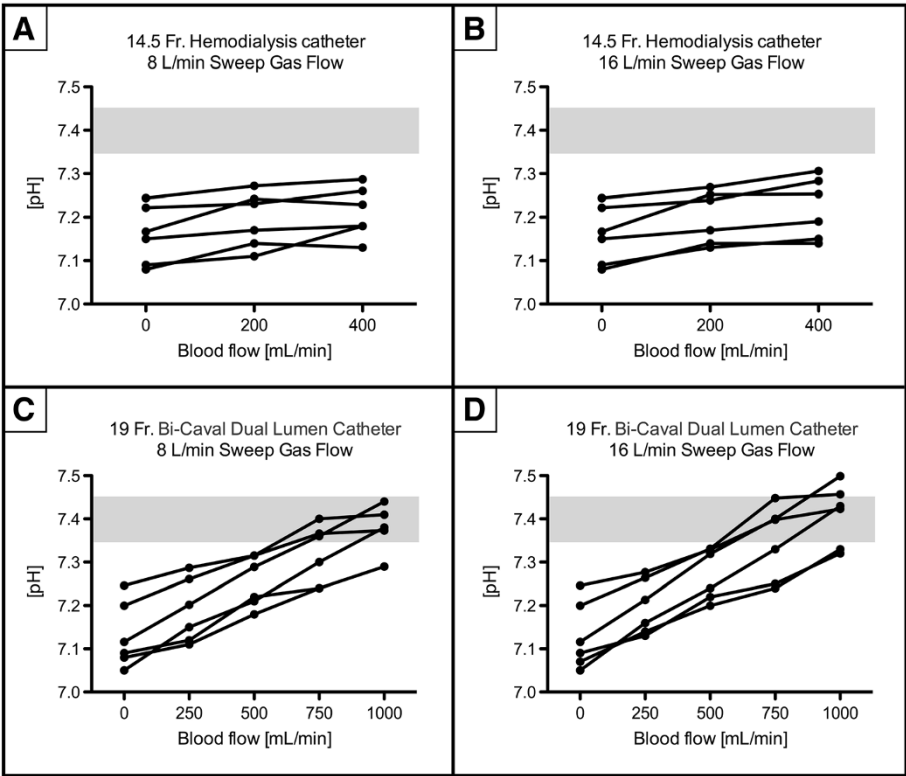
In the 1970's, Kolobow [26] and Gattinoni [27] indicated that ECCO<sub>2</sub>R is dependent not only on venous PCO<sub>2</sub>, blood flow and sweep gas flow, but also on the size of the oxygenator. The currently used oxygenator provides a surface area of 0.98 m<sup>2</sup> without heat exchange fibers. The high efficiency of the system is reflected by a very low mean PaCO<sub>2</sub> value, leading to alkalotic pH values in the blood that is delivered by the oxygenator at

low blood flow rates. This may explain why the previously described linear relationship between sweep gas flow and ECCO<sub>2</sub>R was not observed [22,24,28]. As shown by the present study, sweep gas flow rates of more than 6 L/minute, but not lower flow rates, can sufficiently maintain an optimal ECCO<sub>2</sub>R when a blood flow rate of 1,000 ml/minute is applied.

Interestingly, ECCO<sub>2</sub>R tended to be more efficient when 100% oxygen was switched to room air sweep gas. As hypercapnic respiratory failure is not necessarily associated with severe hypoxemia, the use of air as a sweep gas may slightly improve the effectiveness of ECCO<sub>2</sub>R, but will also reduce the oxygen transfer capacity of the extracorporeal support. On the other hand, the application of oxygen sweep gas was sufficient to improve oxygenation when the ratio of catheter blood flow rate to cardiac output was relatively high, in line with previous results [24].

The current study has some limitations. First, data acquired in animals cannot automatically be transferred into a clinical setting; however, the animals showed CO<sub>2</sub> production and cardiac output rates that were similar to those observed in adult humans. Previous studies in humans have already shown the clinical effects of ECCO<sub>2</sub>R;





**Figure 3** pH dependence on blood flow. **A)** 14.5Fr catheter; 8 L/minute sweep gas flow. **B)** 14.5Fr catheter; 16 L/minute sweep gas flow. **C)** 19Fr catheter; 8 L/minute sweep gas flow. **D)** 19Fr catheter; 16 L/minute sweep gas flow. Fr, French.

thus, the present data are likely to be helpful in understanding the physiology of ECCO<sub>2</sub>R in humans as well. Furthermore, the anatomy of the pig is not comparable to a human adult, and the catheters we used may not be ideal in clinical practice. However, the perfect cannula for CO<sub>2</sub> removal still has to be designed. Second, the typical clinical scenario of exacerbated COPD with severe airflow limitation was not simulated, since a rather high dead space ventilation protocol was used to artificially increase PaCO<sub>2</sub>. Therefore, the interaction between ECCO<sub>2</sub>R and mechanical ventilation could not be investigated. This, however, is suggested to be of clinical importance, since severe airflow limitation frequently requires the adaptation of ventilator

settings. This, in turn, can lead to reduced alveolar ventilation that potentially impacts on acidosis. Third, the present study only applied short-term ECCO<sub>2</sub>R. In a real-life setting, the long-term effects of blood flow, cannula size and sweep gas flow application need to be elucidated, since CO<sub>2</sub> is also stored in the form of HCO<sub>3</sub> in slow compartments, and it may take several hours until a steady-state is reached. This is particularly pertinent to patients with acute-on-chronic ventilatory failure who present with respiratory acidosis, hypercapnia and high bicarbonate levels. On the other hand, the time constant for reducing blood CO<sub>2</sub> in patients by ventilation is 10 minutes

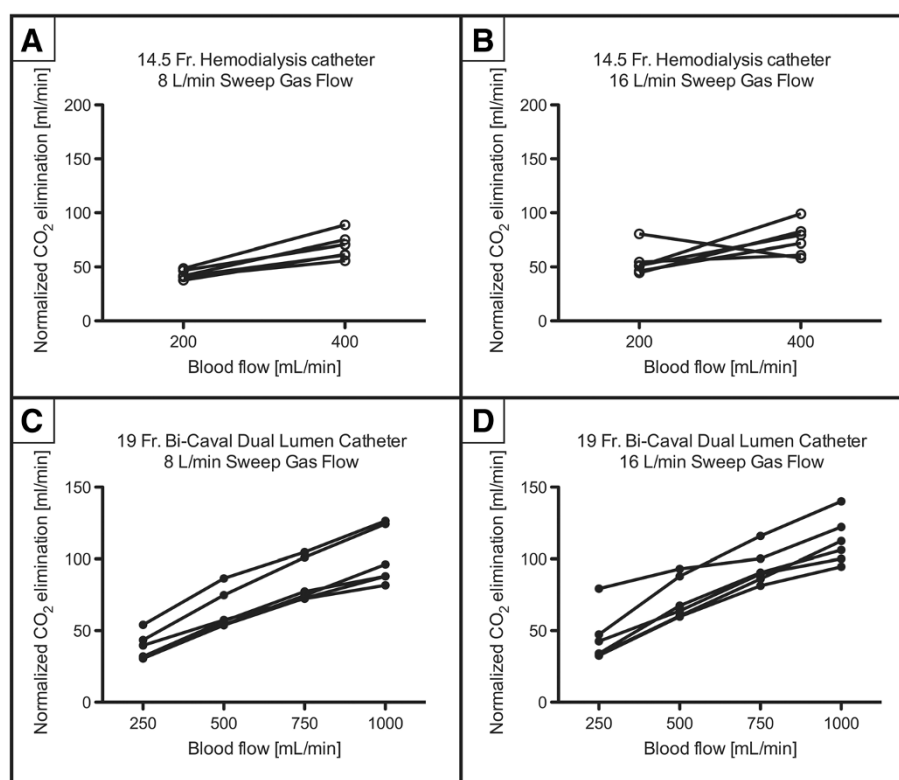
**Table 2** 14.5Fr hemodialysis catheter, sweep gas flow 16 L/minute

Blood flow [ml/min]	CO <sub>2</sub> elimination [ml/min]	PaCO <sub>2</sub> [mmHg]	pH	PaO <sub>2</sub> [mmHg]
0	0	91.3 ± 11.6	7.16 ± 0.07	137.1 ± 26.8
200	62.4 ± 12.2	85.6 ± 12.0	7.20 ± 0.06	167.6 ± 27.4
400	77.9 ± 17.4	82.3 ± 15.0	7.22 ± 0.07	173.3 ± 21.6

Fr, French; PaCO<sub>2</sub>, partial pressure of CO<sub>2</sub> in arterial blood; PaO<sub>2</sub>, partial pressure of O<sub>2</sub> in the arterial blood.

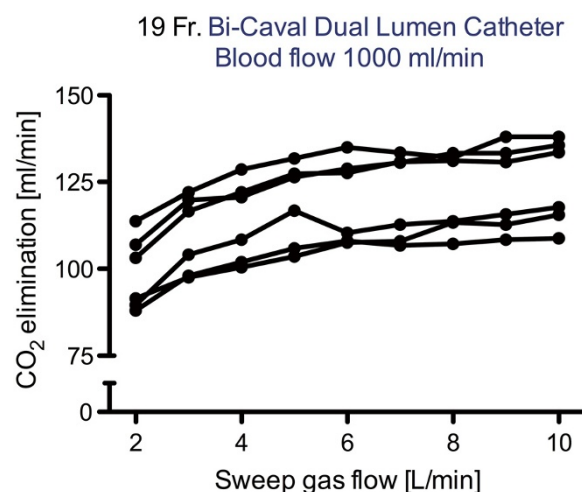
**Table 3** 19Fr Bicaval Dual Lumen Catheter, sweep gas flow 16 L/minute

Blood flow [ml/min]	CO <sub>2</sub> elimination [ml/min]	PaCO <sub>2</sub> [mmHg]	pH	PaO <sub>2</sub> [mmHg]
0	0	107.9 ± 20.7	7.13 ± 0.08	122.9 ± 29.4
250	83.4 ± 11.8	90.3 ± 13.5	7.20 ± 0.06	142.8 ± 35.8
500	118.7 ± 23.9	76.9 ± 9.6	7.27 ± 0.06	165.3 ± 39.8
750	138.3 ± 22.8	66.9 ± 11.1	7.34 ± 0.09	182.0 ± 42.6
1,000	146.1 ± 22.6	55.7 ± 10.5	7.41 ± 0.07	193.6 ± 41.0



**Figure 4** Normalized elimination of carbon dioxide (CO<sub>2</sub>) depending on blood flow. **A)** 14.5Fr catheter; 8 L/minute sweep gas flow. **B)** 14.5Fr catheter; 16 L/minute sweep gas flow. **C)** 19Fr catheter; 8 L/minute sweep gas flow. **D)** 19Fr catheter; 16 L/minute sweep gas flow.

[29]; therefore, 15 minutes at each setting should have been an adequate amount of time to detect any changes in PaCO<sub>2</sub>. Furthermore, in the present study we did not put the focus on anticoagulation since clotting was no issue in our short-term experiments of 12 hours duration.

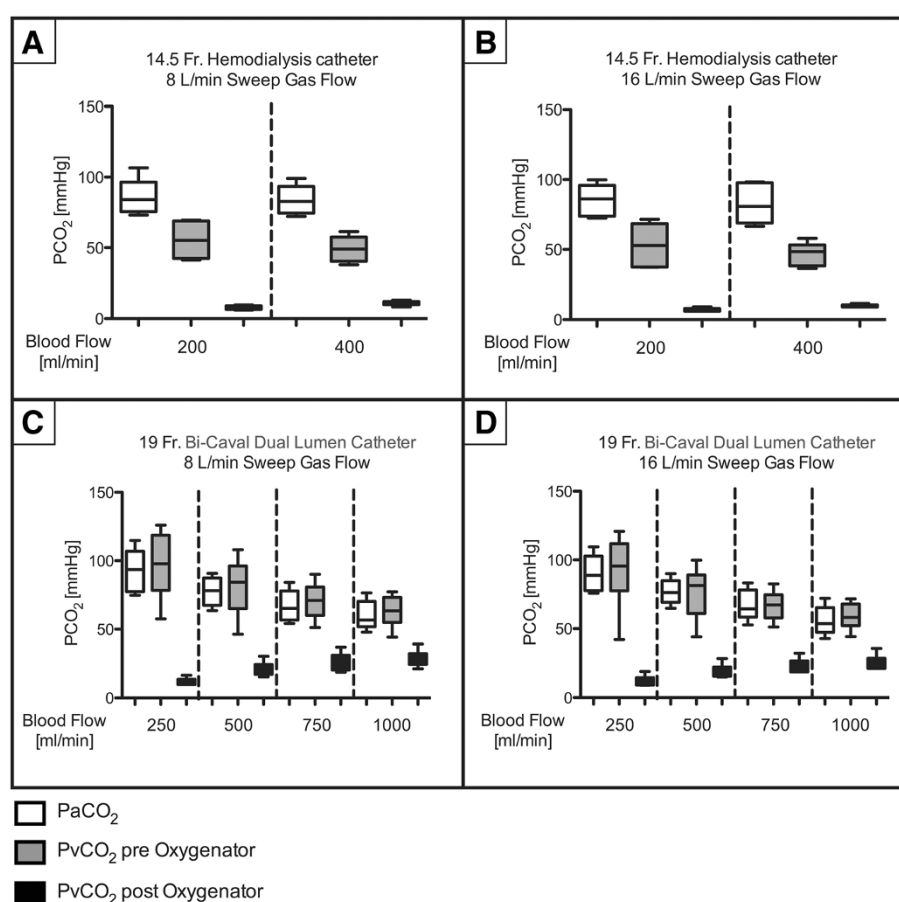


**Figure 5** Elimination of carbon dioxide (CO<sub>2</sub>) in dependence of sweep gas flow under a fixed blood flow of 1,000 ml/minute using a 19Fr catheter. Fr, French.

Further studies have to be done in humans, since low-flow devices may need more anticoagulation in comparison to high-flow extracorporeal membrane oxygenation (ECMO). Finally, only one system for ECCO<sub>2</sub>R was tested in the present study, and this is suggested to limit the comparison of the current trial with other trials, in which different systems have been used. Nevertheless, the currently used system has shown to be highly effective for ECCO<sub>2</sub>R represented by a PCO<sub>2</sub> lower than 10 mmHg and a PO<sub>2</sub> of 600 mmHg after the oxygenator with low blood flows. Although other systems function in a different way, it is physically difficult to further lower PCO<sub>2</sub>. Thus, we believe that the present study is valid to systematically show changes in physiology during ECCO<sub>2</sub>R when using different conditions.

## Conclusions

In conclusion, this animal study has shown that severe respiratory acidosis can be successfully managed by venovenous ECCO<sub>2</sub>R, but only when blood flow rates ranging between 750 and 1,000 ml/minute are applied. For this purpose, the use of specifically-designed catheters with an inner diameter greater than that of the typical hemodialysis catheters are required to establish flow rates ranging between 750 and 1,000 ml/minute and to



**Figure 6** Partial pressure of arterial (PaCO<sub>2</sub>) and venous (PvCO<sub>2</sub>) carbon dioxide depending on blood flow, sweep gas flow and cannula size. **A)** 14.5Fr catheter; 8 L/minute sweep gas flow. **B)** 14.5Fr catheter; 16 L/minute sweep gas flow. **C)** 19Fr catheter; 8 L/minute sweep gas flow. **D)** 19Fr catheter; 16 L/minute sweep gas flow. Fr, French.

avoid blood recirculation. In addition, the study has shown that a sweep gas flow rate above 6 L/minute is of minor importance for ECCO<sub>2</sub>R when using modern, highly-efficient oxygenators with low blood-flow rates. This holds true for the system tested, which is highly effective, represented by a PvCO<sub>2</sub> of 10 to 30 mmHg after the oxygenator and, therefore, may be translated to comparable systems. This study also suggests that low-flow veno-venous ECCO<sub>2</sub>R with modern miniaturized membrane lungs can serve as a treatment option for severe respiratory acidosis associated with acute respiratory failure and severe hypercapnia. Whether these techniques prove to be suitable to avoid endotracheal intubation or to facilitate early extubation in intubated patients needs to be elucidated by future clinical trials.

## Key messages

- Severe respiratory acidosis with pH values of 7.0 to 7.2 can be successfully managed by veno-venous ECCO<sub>2</sub>R.

- For this purpose, blood flow rates ranging between 750 and 1,000 ml/minute are mandatory.
- Specifically-designed catheters aimed at avoiding blood recirculation warranting the target blood flow are required.
- Sweep gas flow rates above 6 L/minute are sufficient for maximal ECCO<sub>2</sub>R.

## Additional file

**Additional file 1: Absolute values of CO<sub>2</sub> elimination and blood gas analysis with a sweep gas flow of 8 L O<sub>2</sub>/minute depending on blood flow.** The table shows the CO<sub>2</sub> elimination capacity of the ECCO<sub>2</sub>R system and the corresponding blood gas analysis with a sweep gas flow of 8 L O<sub>2</sub>/minute with a hemodialysis catheter (**A**) and the 19Fr Bicaval Dual Lumen Catheter (**B**) according to different blood flow levels. It is clearly shown that ECCO<sub>2</sub>R is less efficient with the 14.5Fr catheter (**A**) compared to the 19Fr Bicaval Dual Lumen Catheter (**B**).

## Abbreviation

ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; ECCO<sub>2</sub>R: extracorporeal CO<sub>2</sub> removal; ECMO: extracorporeal membrane oxygenation; Fr: French; PaCO<sub>2</sub>: partial



pressure of CO<sub>2</sub> in arterial blood; PALP: pump assisted lung protection; PCO<sub>2</sub>: partial pressure of CO<sub>2</sub>; PEEP: positive end expiratory pressure; PVC<sub>2</sub>: partial pressure of CO<sub>2</sub> in venous blood; NIV: non-invasive ventilation.

### Competing interests

CK received travel grants and lecture fees from Maquet, Rastatt, Germany. KK, GH and AL have no competing interests. FSS performs consultant services for Maquet Critical Care, Sweden. WW received fees for advisory board meetings and lectures from Maquet, Rastatt, Germany. TM received travel grants from Maquet, Rastatt, Germany. All authors declare that they have no non-financial competing interests.

### Authors' contributions

CK designed the study (together with KA and TM). CK, FS and AL performed the animal experiments and analyzed the physiological data (together with TM and WW). GH designed and supervised the study and the analysis of results. WW and CK designed the concept of the manuscript; all the other authors (CK, KA, FS, AL, GH, TM) contributed to the final drafting of the manuscript. All authors read and approved the final manuscript.

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### References

- Lightowler JV, Wedzicha JA, Elliott MW, Ram FS: **Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis.** *BMJ* 2003, **326**:185.
- Chandra D, Stamm JA, Taylor B, Ramos RM, Satterwhite L, Krishnan JA, Mannino D, Sciruba FC, Holguin F: **Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998–2008.** *Am J Respir Crit Care Med* 2012, **185**:152–159.
- Hoo GW, Hakimian N, Santiago SM: **Hypercapnic respiratory failure in COPD patients: response to therapy.** *Chest* 2000, **117**:169–177.
- Quinnell TG, Pilsworth S, Shneerson JM, Smith IE: **Prolonged invasive ventilation following acute ventilatory failure in COPD: weaning results, survival, and the role of noninvasive ventilation.** *Chest* 2006, **129**:133–139.
- Ambrosino N, Vaghegchini G: **Noninvasive positive pressure ventilation in the acute care setting: where are we?** *Eur Respir J* 2008, **31**:874–886.
- Conti G, Antonelli M, Navalesi P, Rocco M, Bui M, Spadetta G, Meduri GU: **Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial.** *Intensive Care Med* 2002, **28**:1701–1707.
- Gattinoni L, Agostoni A, Pesenti A, Pelizzola A, Rossi GP, Langer M, Vesconi S, Uziel L, Fox U, Longoni F, Kolobow T, Damia G: **Treatment of acute respiratory failure with low-frequency positive-pressure ventilation and extracorporeal removal of CO<sub>2</sub>.** *Lancet* 1980, **2**:292–294.
- Gattinoni L, Kolobow T, Tomlinson T, Iapichino G, Samaja M, White D, Pierce J: **Low-frequency positive pressure ventilation with extracorporeal carbon dioxide removal (LFPPV-ECCO2R): an experimental study.** *Anesth Analg* 1978, **57**:470–477.
- Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Birocco A, Faggiano C, Quintel M, Gattinoni L, Ranieri VM: **Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal.** *Anesthesiology* 2009, **111**:826–835.
- Bein T, Weber-Carstens S, Goldmann A, Muller T, Staudinger T, Brederlau J, Muellenbach R, Dembinski R, Graf BM, Wewalka M, Philipp A, Wernecke KD, Lubnow M, Slutsky AS: **Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO<sub>2</sub> removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study.** *Intensive Care Med* 2013, **39**:847–856.
- Livigni S, Maio M, Ferretti E, Longobardo A, Potenza R, Rivalta L, Selvaggi P, Vergano M, Bertolini G: **Efficacy and safety of a low-flow veno-venous carbon dioxide removal device: results of an experimental study in adult sheep.** *Crit Care* 2006, **10**:R151.
- Batchinsky AI, Jordan BS, Regn D, Necsoiu C, Federspiel WJ, Morris MJ, Cancio LC: **Respiratory dialysis: reduction in dependence on mechanical ventilation by venovenous extracorporeal CO<sub>2</sub> removal.** *Crit Care Med* 2011, **39**:1382–1387.
- Kluge S, Braune SA, Engel M, Nierhaus A, Frings D, Ebel H, Uhrig A, Metschke M, Wegscheider K, Suttrop N, Rousseau S: **Avoiding invasive mechanical ventilation by extracorporeal carbon dioxide removal in patients failing noninvasive ventilation.** *Intensive Care Med* 2012, **38**:1632–1639.
- Muller T, Lubnow M, Philipp A, Bein T, Jeron A, Luchner A, Rupprecht L, Reng M, Langgartner J, Wrede CE, Zimmermann M, Birnbaum D, Schmid C, Riegger GA, Pfeifer M: **Extracorporeal pumpless interventional lung assist in clinical practice: determinants of efficacy.** *Eur Respir J* 2009, **33**:551–558.
- Moerer O, Quintel M: **Protective and ultra-protective ventilation: using pumpless interventional lung assist (iLA).** *Minerva Anestesiol* 2011, **77**:537–544.
- Bein T, Weber F, Philipp A, Prasser C, Pfeifer M, Schmid FX, Butz B, Birnbaum D, Taeger K, Schlitt HJ: **A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia.** *Crit Care Med* 2006, **34**:1372–1377.
- Burki NK, Mani RK, Herth FJ, Schmidt W, Teschler H, Bonin F, Becker H, Randerath WJ, Stieglitz S, Hagmeyer L, Priegnitz C, Pfeifer M, Blaas SH, Putensen C, Theuerkauf N, Quintel M, Moerer O: **A novel extracorporeal CO<sub>2</sub> removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD.** *Chest* 2013, **143**:678–686.
- Abrams DC, Brenner K, Burkart KM, Agerstrand CL, Thomashow BM, Bacchetta M, Brodie D: **Pilot study of extracorporeal carbon dioxide removal to facilitate extubation and ambulation in exacerbations of chronic obstructive pulmonary disease.** *Ann Am Thorac Soc* 2013, **10**:307–314.
- van Milgen J, Noblet J, Dubois S, Bernier JF: **Dynamic aspects of oxygen consumption and carbon dioxide production in swine.** *Br J Nutr* 1997, **78**:397–410.
- Wearden PD, Federspiel WJ, Morley SW, Rosenberg M, Bieniek PD, Lund LW, Ochs BD: **Respiratory dialysis with an active-mixing extracorporeal carbon dioxide removal system in a chronic sheep study.** *Intensive Care Med* 2012, **38**:1705–1711.
- Gattinoni L, Pesenti A, Mascheroni D, Marcolin R, Fumagalli R, Rossi F, Iapichino G, Romagnoli G, Uziel L, Agostoni A, Kolobow T, Giorgio D: **Low-frequency positive-pressure ventilation with extracorporeal CO<sub>2</sub> removal in severe acute respiratory failure.** *JAMA* 1986, **256**:881–886.
- Karagiannidis C, Lubnow M, Philipp A, Riegger GA, Schmid C, Pfeifer M, Mueller T: **Autoregulation of ventilation with neurally adjusted ventilatory assist on extracorporeal lung support.** *Intensive Care Med* 2010, **36**:2038–2044.
- Cardenas VJ Jr, Miller L, Lynch JE, Anderson MJ, Zwischenberger JB: **Percutaneous venovenous CO<sub>2</sub> removal with regional anticoagulation in an ovine model.** *ASAIO J* 2006, **52**:467–470.
- Schmidt M, Tachon G, Devilliers C, Muller G, Hekimian G, Brechot N, Merceron S, Luyt CE, Trouillet JL, Chastre J, Leprince P, Combes A: **Blood oxygenation and decarboxylation determinants during venovenous ECMO for respiratory failure in adults.** *Intensive Care Med* 2013, **39**:838–846.
- Korver EP, Ganushchak YM, Simons AP, Donker DW, Maessen JG, Weerwind PW: **Quantification of recirculation as an adjuvant to transthoracic echocardiography for optimization of dual-lumen extracorporeal life support.** *Intensive Care Med* 2012, **38**:906–909.

26. Kolobow T, Gattinoni L, Tomlinson TA, Pierce JE: **Control of breathing using an extracorporeal membrane lung.** *Anesthesiology* 1977, **46**:138–141.
27. Gattinoni L, Kolobow T, Tomlinson T, White D, Pierce J: **Control of intermittent positive pressure breathing (IPPB) by extracorporeal removal of carbon dioxide.** *Br J Anaesth* 1978, **50**:753–758.
28. Park M, Costa EL, Maciel AT, Silva DP, Friedrich N, Barbosa EV, Hirota AS, Schettino G, Azevedo LC: **Determinants of oxygen and carbon dioxide transfer during extracorporeal membrane oxygenation in an experimental model of multiple organ dysfunction syndrome.** *PLoS One* 2013, **8**:e54954.
29. Taskar V, John J, Larsson A, Wetterberg T, Jonson B: **Dynamics of carbon dioxide elimination following ventilator resetting.** *Chest* 1995, **108**:196–202.

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